Remarks

Claim status. Claims 1, 2, 4, 6, 28, and 30 are now in the case. Claim 1 has been amended. Claims 5 and 7 to 16 have been canceled. The amendment to Claim 1 is supported at page 2, lines 10 to 17; page 3, line 12; and page 14, lines 3 to 7.

In the Office Action, the Examiner alleged incorporation of essential material by reference and lack of enablement under 35 U.S.C. Section 112.

Regarding incorporation by reference, it would only be improper if the incorporated material were "essential" as defined in MPEP Section 608.01(p). That section states that to be essential, the material must either (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode. Here, the invention concerns the correction of folding in Fc-linked IL-1ra protein. The details of this invention are disclosed in the specification, not the cited references. The incorporated subject matter does not fall within any of the three categories under MPEP Section 608.01(p).

Under Section 112, the Examiner argued several of the factors under *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). At the outset, the Examiner argued that the quantity of experimentation was "great, on the order of several man-years" (Office Action at paragraph no. 8, page 4). The Examiner failed, however, to provide any supporting evidence for this belief. Moreover, that argument seems unfounded in view of the limitation of the claims to IL-1ra protein.

The Examiner alleged that the amount of guidance is "to a great extent reliant upon the impropoer incorporation by reference" of several references. The cited references do not concern the claimed invention, as noted above. Moreover, for the claimed process, there is sufficient detail presented in the specification and, indeed, in Claim 1 itself. The working examples concern a related molecule (another Fc fusion protein) and they describe the process in detail. Claim 1 itself describes the reagent employed with reasonable specificity as a copper (II) halide and further provides the concentration.

The Examiner noted that the working examples were not directed to the elected species, concluding that the invention does not set forth the starting materials and reaction conditions that must be employed. This argument ignores the guidance provided by the working examples as well as all parts of the specification outside of the working examples. As now claimed, the invention is clearly directed toward IL-1ra, which is known in the art. The most important reaction condition (copper halide concentration) is noted clearly in the specification and also in the broadest claim. The invention is directed toward correct folding of an Fc domain, which is part of the molecule prepared in the working examples even if the entire molecule in the claim is not identical to that in the working examples.

The Examiner cited the nature of the invention, declaring that "matters of physiology and chemistry ... are inherently unpredictable...." (Office Action at page 6). Taken on its face, the Examiner's stance would not allow for any amount of experimentation. A more reasonable view is as shown in the language quoted by the Examiner from

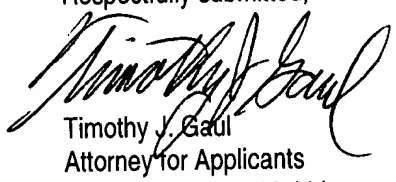
In re Fisher, "[T]he scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." The present case is *not* the substitution of an entirely different reagent or substrate in the claims over the working examples. Here, the substrate is a macromolecule, a fusion protein. That part of the fusion protein that is acted upon in the claimed process (i.e., the Fc domain) is present in both the substrate of the claims and of the working examples. The Examiner has not presented any reason to doubt some level of predictability from one Fc fusion protein to another.

The Examiner alleged that the state of the prior art concerning IL-1ra is "extremely limited" (Office Action at page 6) without providing any supporting evidence for this conclusion. Contrary to the Examiner's belief, IL-1ra has been known for over ten years and, as a drug in human clinical trials, was extensively characterized. See, for example, Arend *et al.*, J. Immunol. , 134(6): 3868-3875 (1985); Seckinger *et al.*, J. Immunol., 139(5): 1546-1549 (1987); Prieur *et al.*, The Lancet , 2: 1240-1242 (1987); Mazzei *et al.*, Eur. J. Immunol., 20: 683-689 (1990); Eisenberg *et al.*, Nature, 343: 341-346 (1990); Hannum *et al.*, Nature, 343(6256): 336-340 (1990); Seckinger *et al.*, J. Immunol., 145(12): 4181-4184 (1990); Schwab *et al.*, Infect. Immun., 59(12): 4436-4442 (1991); Lebsack *et al.*, Arthritis Rheum., 34(suppl): S67 (1991); Firestein *et al.*, J. Immunol., 149(3): 1054-1062 (1992); Deleuran *et al.*, Br. J. Rheumatol., 31: 801-809 (1992). Variants and derivatives of IL-1ra have been disclosed, as well; see U.S. Patent No. 5,075,222; WO 97/28828. A recombinant form of IL-1ra produced in *E. coli* was approved for marketing by the U.S. Food and Drug Administration in 2001 under the trade name Kineret™. Thus, the Examiner's unsupported assumption of a limited state of the prior art is at odds with the scientific and patent literature.

The Examiner cited the breadth and scope of the claims, alleging that the specification did not provide an adequate description showing that the applicant possessed the starting materials. Here, the claims are drawn to a well-defined starting material and does not extend to so vast a class as to require undue experimentation.

In light of the foregoing amendments and remarks, the Applicants respectfully request entry of all amendments, withdrawal of all objections and rejections, and allowance of all claims.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

At page 19 , line 22:

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 3);

At page 19 , line 23

$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 4);

At page 19 , line 24:

$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 5); and

At page 19 , line 25, replace with the following:

GlyProAsnGlyGly (SEQ ID NO: 6).

At page 27, lines 18-29:

Pharmaceutical Compositions

In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (*e.g.*, ~~Tween~~ TWEEN™ 80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite),

Claims:

1. (Amended). A process for preparing a pharmacologically active compound, which comprises:

(a) preparing a pharmacologically active compound comprising an Fc domain in *E. coli*;

(b) treating the pharmacologically active compound with a copper (II) halide in a concentration of at least about 10 m*M*; and

(c) isolating the treated fusion molecule;

wherein the pharmacologically active compound is an IL-1ra protein.